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## **Improving outcomes in congenital cataract**

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Dear Editors,

Opening statement / abstract:

Lin et al.<sup>1</sup> report novel insights into the biology of the phenomenon with which paediatric ophthalmologists battle, ie lens regeneration after cataract surgery in infants. They then take the interesting approach of considering whether, using a different surgical technique, it is possible to convert this 'post-operative complication'

into an alternative therapy for children aged under 24 months old.<sup>1</sup> However, the early outcomes reported for the experimental group fall far short of expected outcomes for this population, ie young children with uncomplicated bilateral congenital cataract, for which the authors offer no comment or explanation.

Regeneration of residual lens cells following surgical removal of congenital cataract can result in reopacification, which needs to be treated by further intraocular surgery, necessitating repeated general anaesthetics during a sensitive period of neurodevelopment. Lin et al's<sup>1</sup> elegant adaptation of this regenerative process, in which a novel 'surgical method of cataract removal preserves endogenous lens cells, achieving functional lens regeneration'<sup>1</sup> may eventually lead to the development of treatments for degenerative disease. However, their report conflates adult cataract (a degenerative process) and congenital and infantile cataract in relation to a number of key issues and resulted in a similar unhelpful conflation in the media coverage of this paper.<sup>2</sup> Cataract is virtually universal in older age, making cataract surgery one of the most common surgical procedures and with enviably excellent visual outcomes. By contrast, infantile cataract is uncommon, affecting 3-15 per 10,000 children worldwide.<sup>3</sup> We now understand that mutations within the genes responsible for the production or orchestration of the lens epithelial progenitor / stem cells (LECs) are responsible for the majority of bilateral congenital or infantile cataract, even in cases where there is no family history.<sup>4</sup> Thus the treatment approach adapted by Lin et al, which relies on regeneration of lens stem cells without addressing the underlying genetic defect, cannot be definitive. Children treated using this technique may require further surgery but Lin et al do not acknowledge this in the article.

The rationale for the trial reported by Lin et al is the need to address adverse outcomes associated with using artificial intraocular lenses but this was not the 'control' standard approach evaluated within the report. Equivalence in vision outcomes between their intervention and control groups was reported, but these should have been assessed against the extant benchmark. Outcomes in infantile cataract have improved substantially over the past few decades, largely due to application of basic neuroscientific understanding of sensitive and critical periods in visual neurodevelopment. Hence whole population newborn screening programmes exist in many countries to ensure early diagnosis and prompt referral for specialist treatment. Younger age at surgery is the most powerful predictor of better visual outcome and the 'window for intervention' in cataract truly present at birth is conventionally considered the first six to eight weeks of life. Late diagnosis/treatment is the key factor in poor visual outcomes due to irreversible amblyopia, as particularly evidence in settings without resource or infrastructure for screening and early specialist intervention. We have previously, on behalf of the British Isles Congenital Cataract Interest Group, reported outcomes within a contemporaneous, nationally representative cohort of children undergoing surgery in the British Isles for congenital and infantile cataract in the first two years of life (IoLunder2 study).<sup>5</sup> Our outcomes are comparable to other contemporary reports,<sup>6</sup> and represents a greater than 2-fold better outcome than that reported by Lin et al in either their experimental or control groups. Indeed, the mean acuity achieved in their trial is the threshold for legal definition of blindness, an outcome that would lead most ophthalmologists, and likely most parents, to question the value of this new proposed intervention.

Cataract related childhood visual impairment is largely due to bilateral deprivation amblyopia, the failure to restore a normal trajectory of visual neurodevelopment during a brief and finite window of opportunity. This critical window closes in the first six months of life. Thereafter, 'successful' treatment stands little chance of good outcome.

Effective treatment for congenital cataract requires, alongside surgery, post-operative management of the impact of the absence of the focusing power of the natural crystalline lens. Failure to appropriately manage the refractive (focusing) state of the post-surgical eye will result in a dense amblyopia. As the method described in Lin et al involves an 8 month post-operative period of partially obscured and poorly focused vision (as the lens regenerates) the inevitable resultant amblyopia may explain the poor visual outcomes, as the authors offer no other explanation, nor described how the rapidly changing and high refractive error (18 Diopters in 8 months) was managed. Had the report adhered to international standard of CONSORT<sup>7</sup> it might be have been possible to assess its quality (internal validity) and generalisability (external validity). For example, it is necessary to know a) whether the control and intervention groups were equivalent with respect to baseline clinical characteristics (particularly age at surgery), b) how randomization was undertaken, c) the power calculation and the primary outcome and secondary outcomes on which this was based, c) how clustering by surgeon was addressed and d) how clustering/correlation of outcomes data was addressed in the analysis, given that both eyes of each subject were treated and analysed. The authors have described their study as a Phase 1 trial, but the aim of such investigation is to assess

adverse outcomes of treatment, such as uncorrected high or irregular refractive outcome, which is amblyogenic.

As the paper stands, it is not possible to agree with its principal conclusion that it provides evidence '*supporting the superiority of the novel treatment*'. A tempered report, clearly articulating the limitations of the approach with respect to outcome and permanency of effect, would have avoided giving the false impression that their approach can be expected to supercede current treatment practices.

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All authors contributed equally to all aspects of authorship

The authors have no competing interests to declare

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